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[Continued on next page]

WO 2003/090690 A3

(54) Title: CELLULAR ACCUMULATION OF PHOSPHONATE ANALOGS OF HIV PROTEASE INHIBITOR COMPOUNDS AND THE COMPOUNDS AS SUCH

(57) Abstract: Phosphonate substituted compounds with HIV protease inhibitory properties having use as therapeutics and for other industrial purposes are disclosed. The compositions inhibit HIV protease activity and/or are useful therapeutically for the treatment of AIDS and other antiviral infections, as well as in assays for the detection of HIV protease.



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(88) Date of publication of the international search report:  
24 June 2004

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/12901A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07F9/40 C07F9/02 C07F9/38

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/04033 A (ARMITAGE IAN GORDON ;SEARLE ANDREW DAVID (GB); GLAXO GROUP LTD (GB) 27 January 2000 (2000-01-27) page 1, paragraph 3; claims 1-4 page 7, line 1 – page 10, line 21; claim 5	1,2
X		130-136
P, A	MENENDEZ-ARIAS L: "Targeting HIV: antiretroviral therapy and development of drug resistance" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER, AMSTERDAM, NL, vol. 23, no. 8, 1 August 2002 (2002-08-01), pages 381-388, XP004386181 ISSN: 0165-6147 Fig.1,3; Tab. 1 the whole document	1-14

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

\*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the International search

10 March 2004

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20.04.2004

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/12901

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Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/11906 A (CHASALOW FRED I ;AMUR PHARMACEUTICALS INC (US)) 26 March 1998 (1998-03-26) page 5, lines 25,26; claim 1 -----	1
A	US 5 750 493 A (SCHINAZI RAYMOND F ET AL) 12 May 1998 (1998-05-12) SC-52151, Formula I -----	1,2
A	ABDEL-MEGUID S S ET AL: "Inhibition of human immunodeficiency virus-1 protease by a C2-symmetric phosphinate. Synthesis and crystallographic analysis" BIOCHEMISTRY 1993 UNITED STATES, vol. 32, no. 31, 1993, pages 7972-7980, XP002257745 ISSN: 0006-2960 .. scheme 1, formula 3, figure 1 -----	1
A	WO 02/14344 A (UNIV KANSAS) 21 February 2002 (2002-02-21) compounds 12, 17b page 1, line 1 - page 6, line 25; examples 6,9,11 -----	1,2, 130-136
A	CLERCQ DE E: "NEW DEVELOPMENTS IN ANTI-HIV CHEMOTHERAPY" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 8, no. 13, November 2001 (2001-11), pages 1543-1572, XP009012547 ISSN: 0929-8673 figure 18 -----	1-3, 15-88, 95,96, 130-136
A	WO 02/06292 A (DU PONT PHARM CO) 24 January 2002 (2002-01-24)  page 17 -----	1-3,5, 15-88, 95,96, 130-136
X	EP 0 441 192 A (BAYER A.-G., GERMANY) 14 August 1991 (1991-08-14) page 31; claims 1,8,10; example 18 -----	3
A	DVORAKOVA, HANA ET AL: "Synthesis of 2'-Aminomethyl Derivatives of 9-(2-(Phosphonomethoxy)ethyl) Nucleotide Analogs as Potential Antiviral Agents" JOURNAL OF MEDICINAL CHEMISTRY , 39(17), 3263-3268 CODEN: JMCMAR; ISSN: 0022-2623, 1996, XP002273095 compounds 7,a,b; table 1 -----	3,135
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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/12901

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 914 332 A (CHEN XIAOQI ET AL) 22 June 1999 (1999-06-22) claims 77,78 -----	1-3
A	US 5 670 497 A (BOLD GUIDO ET AL) 23 September 1997 (1997-09-23) examples, abstract -----	3
A	WO 96/14314 A (GILEAD SCIENCES, INC., USA) 17 May 1996 (1996-05-17) examples claim 27 & DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BISCHOFBERGER, NORBERT W. ET AL: "Preparation of thiepane sugars for inhibiting and detecting HIV protease" retrieved from STN Database accession no. 1996:469502 abstract -----	3
A	US 2001/031773 A1 (CAMDEN, JAMES BERGER) 18 October 2001 (2001-10-18) paragraph '0058! -----	1-3

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/12901

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 130–133, 136 because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 130–133, 136 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: 92–94, 137–174, 178–200 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,  
no additional fees are to be refunded.

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  
1–91, 95–122, 130–136
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 130-133, 136 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.2

Claims Nos.: 92-94, 137-174, 178-200

In view of the large number and also the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible.

The objections are:

Claim 137 refers back to claim 1 but in claim 1 there is no definition for A3.

In claims 92, and 166 "MBF" is not clear to the skilled person; see for instance WO-A-0114361:  
"Example 2: Preparation of Monobenzyl fluorescein (MBF)"

There is no category for a claim directed to an "improvement"; see claim 138 in connection with Guidelines Ch. III. 3.1.

Apart from the fact that the expressions "improvement" or "improved" as such are unclear, the claims 137-165, 178-184 attempt to define the subject-matter in terms of that unclear result to be achieved which merely amounts to a statement of the underlying (unclear) problem. The technical features necessary for achieving this result should have been added.

Claims 189 - 192, 197-199 relate to an undefined pharmaceutical activity which is not in accordance with the requirements of Art. 6 PCT.

The meaning of "half-life" in claims 178- 184, 196 is not precise; see Guidelines Ch. IV. 4.5.

A claim should be understandable without reference to the description. Therefore, claims 166-174, 185 - 188, and 193-195, 200 cannot be accepted under Art. 6, PCT; Rule 6.2(a) and Guidelines Ch. III. 4.10.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: partly: 1,2,130-134,136

Saquinavir - like HIV protease inhibitor compounds and their use

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2. claims: partly: 1,2,130-134,136

Lopinavir- like HIV protease inhibitor compounds and their use

---

3. claims: partly: 1,2,130-134,136

Ritonavir- like HIV protease inhibitor compounds and their use

---

4. claims: partly: 1,2,130-134,136

Indinavir - like HIV protease inhibitor compounds and their use

---

5. claims: partly: 1,2,130-134,136

Atazanavir - like HIV protease inhibitor compounds and their use

---

6. claims: partly: 1,2,130-134,136

Nelvinavir - like HIV protease inhibitor compounds and their use

---

7. claims: partly: 1,2,130-134,136

Tipranavir - like HIV protease inhibitor compounds and their use

---

8. claims: partly: 1,2,130-134,136

Amprenavir - like HIV protease inhibitor compounds and their use

---

9. claims: partly: 1,2,130-134,136

KNI - like HIV protease inhibitor compounds and their use

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. claims: partly: 1,2,130-134,136

Cyclic carbonyl - like HIV protease inhibitor compounds and  
their use

11. claims: partly: 1,130-134,136

HIV protease inhibitor compounds comprising a phosphonate  
group which are not comprised by inventions 1-10 and their  
use

12. claims: 4, partly: claims 3, 15-88, 95, 96,135

compounds of formula I according to claim 3

13. claims: 5, 89-91, 97-113, partly: claims 3,5, 15-88, 95, 96,135

compounds of formula II according to claim 3

14. claims: 6, partly: claims 3, 15-88, 95, 96,135

compounds of formula III according to claim 3

15. claims: 7, partly: claims 3, 15-88, 95, 96,135

compounds of formula IV according to claim 3

16. claims: partly: claims 3,8, 15-88, 95, 96,135

compounds of formula V according to claim 3

17. claims: partly: claims 3,8, 15-88, 95, 96,135

compounds of formula Va according to claim 3

18. claims: 9, partly: claims 3, 15-88, 95, 96,135

compounds of formula VI according to claim 3

19. claims: 10, partly: claims 3,15-88, 95, 96,135

compounds of formula VII according to claim 3

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

20. claims: 11, 114, 115, 118-122, partly: claims 3, 15-88, 95, 96, 135

compounds of formula VIIa according to claim 3

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21. claims: 12, partly: claims 3, 15-88, 95, 96, 135

compounds of formula VIIb according to claim 3

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22. claims: 13, partly: claims 3, 15-88, 95, 96, 135

compounds of formula VIIc according to claim 3

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23. claims: 14, partly: claims 3, 15-88, 95, 96, 135

compounds of formula VIId according to claim 3

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24. claims: partly: 123-129

compounds of formula I according to claim 123

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25. claims: partly: 123-129

compounds of formula II according to claim 123

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26. claims: partly: 123-129

compounds of formula III according to claim 123

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27. claims: partly: 123-129

compounds of formula IV according to claim 123

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28. claims: partly: 123-129

compounds of formula V according to claim 123

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29. claims: partly: 123-129

compounds of formula VI according to claim 123

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30. claims: partly: 123-129

compounds of formula VII according to claim 123

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

31. claims: partly: 123-129  
compounds of formula VIIa according to claim 123  
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32. claims: partly: 123-129  
compounds of formula VIIb according to claim 123  
---
33. claims: partly: 123-129  
compounds of formula VIIc according to claim 123  
---
34. claims: partly: 123-129  
compounds of formula VIIId according to claim 123  
---
35. claim: partly: 175  
HIV protease inhibitor compounds not comprising a phosphonate or phosphonate prodrug capable of accumulating in human PBMC's  
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36. claims: 176-184, partly: 175  
HIV protease inhibitor compounds comprising a phosphonate or phosphonate prodrug capable of accumulating in human PBMC's  
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International Application No

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